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(54) **[Title of the invention]**

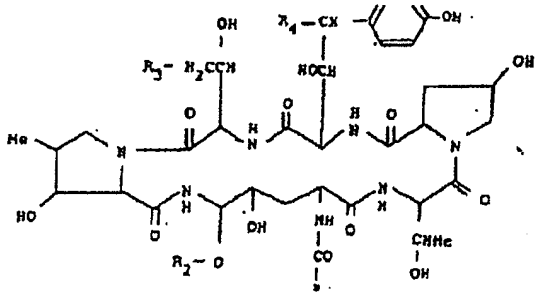
Fat emulsions containing an aculeacin compound

(57) **[Abstract]**

[Object] The purpose is to offer preparations with good stability which have a high therapeutic effect with few adverse reactions as a prophylactic or therapeutic agent against *Pneumocystis carinii* pneumonia, and enable administration of a high content of the active ingredient.

[Constitution] The present invention concerns fat emulsions containing an aculeacin compound, characterized in that they contain a phospholipid, a liquid triglyceride, an aqueous medium and at least one active ingredient selected from a set comprising aculeacin compounds represented by general formula (1)

[Formula 1]



(1)

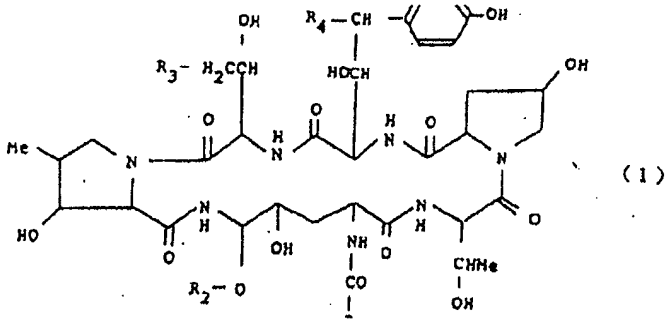
(In the formula, R_1-CO- indicates a long-chain saturated or unsaturated fatty acid residue or a residue of an organic acid, which may contain a benzene ring, pyridine ring, oxygen atom, iodine atom or nitrogen atom in the molecule thereof; R_2 indicates a hydrogen atom, a lower alkyl group which may be branched, a benzyl group or an amino(lower alkyl) group

wherein the amino group may be monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups; R_3 indicates a hydrogen atom or $-CONH_2$; and R_4 indicates a hydrogen atom or hydroxyl group).

[Scope of the Patent Claims]

[Claim 1] Fat emulsion containing an aculeacin compound, characterized in that it contains a phospholipid, a liquid triglyceride, an aqueous medium and at least one active ingredient selected from a set comprising aculeacin compounds represented by general formula (1)

[Formula 1]



(1)

(In the formula, R_1-CO- indicates a long-chain saturated or unsaturated fatty acid residue or a residue of an organic acid, which may contain a benzene ring, pyridine ring, oxygen atom, iodine atom or nitrogen atom in the molecule thereof; R_2 indicates a hydrogen atom, a lower alkyl group which may be branched, a benzyl group or an amino(lower alkyl) group wherein the amino group may be monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups; R_3

indicates a hydrogen atom or $-CONH_2$; and R_4 indicates a hydrogen atom or hydroxyl group).

[Claim 2] Fat emulsion according to claim 1 wherein, in the fat emulsion, the active ingredient is 0.001-50 mg/ml in said emulsion, and there is 0.01-1 part by weight of phospholipid and 2-100 parts by weight of aqueous medium to 1 part by weight of liquid triglyceride.

[Claim 3] Fat emulsion according to claim 1 which is an aculeacin derivative wherein in the aculeacin compound represented by general formula (1) R_1-CO- is a long-chain saturated or unsaturated fatty acid residue, R_2 is a hydrogen atom, R_3 is a hydrogen atom and R_4 is a hydrogen atom or a hydroxyl group.

[Claim 4] Fat emulsion according to claim 1 which is aculeacin Aα, wherein in claim 3 R_1-CO- indicates a myristic acid residue (C14) and R_4 indicates a hydroxyl group.

[Claim 5] Fat emulsion according to claim 1 which is aculeacin Aγ, wherein in claim 3 R_1-CO- indicates a palmitic acid residue (C16) and R_4 indicates a hydroxyl group.

[Claim 6] Fat emulsion according to claim 1 which is aculeacin Dα, wherein in claim 3 R_1-CO- indicates a myristic acid residue (C14) and R_4 indicates a hydrogen atom.

[Claim 7] Fat emulsion according to claim 1 which is aculeacin Dγ, wherein in claim 3 R_1-CO- indicates a palmitic acid residue (C16) and R_4 indicates a hydrogen atom.

[Claim 8] Fat emulsion according to claim 1 wherein the phospholipid is purified lecithin.

[Claim 9] Fat emulsion according to claim 1 wherein the aqueous medium is water or an aqueous solution containing a polyhydric alcohol.

[Claim 10] Fat emulsion according to claim 1 wherein the liquid triglyceride is soybean oil or a medium-chain fatty acid triglyceride.

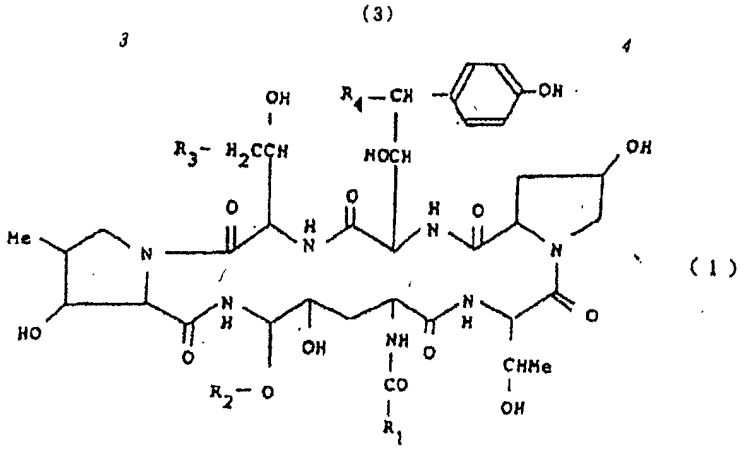
[Detailed description of the invention]

[0001]

[Field of industrial application] The present invention relates to fat emulsions containing an aculeacin compound, characterized in that they contain a phospholipid, a liquid triglyceride, an aqueous medium and at least one active ingredient selected from a set comprising aculeacin compounds represented by general formula (1)

[0002]

[Formula 2]



(1)

[0003] (In the formula, R_1-CO- indicates a long-chain saturated or unsaturated fatty acid residue or a residue of an organic acid, which may contain a benzene ring, pyridine ring, oxygen atom, iodine atom or nitrogen atom in the molecule thereof; R_2 indicates a hydrogen atom, a lower alkyl group which may be branched, a benzyl group or an amino(lower alkyl) group wherein the amino group may be monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups; R_3 indicates a hydrogen atom or $-CONH_2$; and R_4 indicates a hydrogen atom or hydroxyl group), and offers liposome preparations of aculeacin compounds efficacious for the prevention and treatment of *Pneumocystis carinii* pneumonia, for example, and a process for producing the same.

[0004]

[Prior art] Although there is discussion as to the taxonomy of *Pneumocystis carinii*, it can be taken to be a species of protozoa, and to date only one species of the genus is known. It is known to be a possible pneumonia pathogen, and development of *Pneumocystis carinii* pneumonia and death due to respiratory insufficiency frequently occurs in cases of infants with lowered immunity due to congenital immunoinsufficiency or poor nutrition, childhood disorders such as acute lymphatic or myelocytic leukemia, autoimmune disorders of the elderly and malignant tumors leading to lung cancer, when large doses of antitumor agents, steroids or immunosuppressants in particular are used, or in case of AIDS

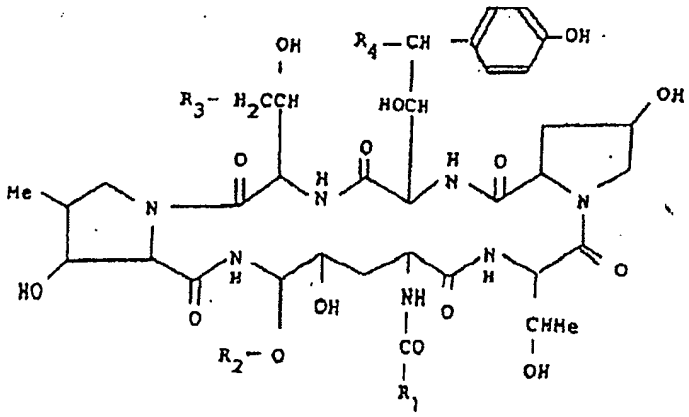
and complicating infections such as toxoplasma, cytomegalovirus, actinomyces or fungi.

[0005] To date, a combination of the antimicrobial agents sulfamethoxazole and trimethoprim (ST), and the antiprotozoal agent pentamidine, have been reported as drugs efficacious against *Pneumocystis carinii* pneumonia; however, sulfa drugs show strong toxicity in AIDS patients and furthermore pentamidine itself shows strong toxicity, so that their use is restricted, with corresponding limitations as regards effectiveness.

[0006] Against this background, preparations containing an aculeacin compound represented by formula (1) below

[0007]

[Formula 3]



(1)

[0008] (In the formula, R_1-CO- indicates a long-chain saturated or unsaturated fatty acid residue or a residue of an organic acid, which may contain a benzene ring, pyridine ring, oxygen atom, iodine atom or nitrogen atom in the molecule thereof; R_2 indicates a hydrogen atom, a lower alkyl group,

which may be branched, a benzyl group or an amino(lower alkyl) group wherein the amino group may be monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups; R_3 indicates a hydrogen atom or $-CONH_2$; and R_4 indicates a hydrogen atom or hydroxyl group), such as the antibiotics aculeacin Aα, Aγ, Dα and Dγ, as an active ingredient have been proposed as preparations with few adverse reactions and a more efficacious therapeutic effect, and from the point of view of formulation, a highly concentrated dosage form of aculeacin compounds is desired.

[0009] However, the aforementioned aculeacin compounds are extremely sparingly soluble in water and liquid triglycerides, and also do not dissolve in chloroform or ether. Although they dissolve in hydrophilic organic solvents, for example alcohols such as methanol, ethanol, isopropanol and *n*-butanol for example, these are unsuitable solvents for injectable preparations. It is also difficult to obtain preparations capable of sustained administration of high concentrations by using cholic acid or synthetic surfactants, etc., as solubilizing agents; and there are also problems as regards safety.

[0010] On the other hand, formulation of sparingly soluble pharmaceutical substances as fat emulsions is known, but sustained administration of high concentrations is impossible with prior fat emulsions; and there is also a method for this sort of sparingly soluble pharmaceutical

substance wherein the sparingly soluble pharmaceutical substance is homogeneously dispersed by dissolving it in a liquid triglyceride using a constitution of a phospholipid, a liquid triglyceride and an aqueous medium, but for this the sparingly soluble pharmaceutical substance needs to dissolve in the liquid triglyceride. However, as mentioned above, aculeacin compounds show hardly any solubility in liquid triglycerides.

[0011]

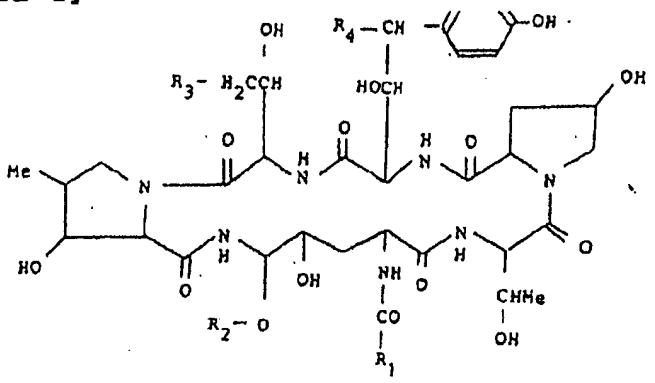
[Problem which the invention is intended to solve] The present invention is a response to the problem above, and the objective thereof is to offer stable fat emulsions containing aculeacin compounds as an active ingredient, as prophylactic and therapeutic agents for *Pneumocystis carinii* pneumonia which are highly safe and easy to use and also enable the administration of high contents of the aforementioned aculeacin compound.

[0012]

[Means for solving the problem and the action thereof] Thus, the present invention concerns fat emulsions containing an aculeacin compound, characterized in that they contain a phospholipid, a liquid triglyceride, an aqueous medium and at least one active ingredient selected from a set comprising aculeacin compounds represented by general formula (1)

[0013]

[Formula 4]



(I)

[0014] (In the formula, R_1-CO- indicates a long-chain saturated or unsaturated fatty acid residue or a residue of an organic acid, which may contain a benzene ring, pyridine ring, oxygen atom, iodine atom or nitrogen atom in the molecule thereof; R_2 indicates a hydrogen atom, a lower alkyl group, which may be branched, a benzyl group or an amino(lower alkyl) group wherein the amino group may be monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups; R_3 indicates a hydrogen atom or $-CONH_2$; and R_4 indicates a hydrogen atom or hydroxyl group).

[0015] Within the present invention, by forming a fat emulsion of the aforementioned active ingredients, which are extremely sparingly soluble in water and liquid triglycerides, the aculeacin compound which is the active ingredient can be contained in the fat emulsion at upwards of the order of 0.001 mg/ml and more particularly at high concentrations of up to the order of 50 mg/ml; the safety of the emulsion is especially good because an aqueous medium is used, a high

concentration of the active ingredient is achieved and it also becomes possible to administer the aforementioned active ingredient efficaciously *in vivo*.

[0016] Within the present invention, the fat emulsion is fine droplets of an O/W emulsion wherein the liquid triglyceride is emulsified by the phospholipid. Ideally it is an emulsion wherein the average size of the oil droplets is 50-300 nm, for example. Within the present invention, the phospholipid can be either a natural phospholipid or a synthetic phospholipid, and ideal examples include purified egg yolk lecithin and purified soybean lecithin. Similarly, there is no specific restriction as to the liquid triglyceride, provided that it is permitted for pharmaceutical use, and ideal examples include soybean oil, sesame oil and synthetic medium-chain fatty acid triglycerides; from the point of view of the stability of the preparation, refined soybean oil and medium-chain fatty acid triclycerides are especially ideal. In addition, additives such as a fatty acid such as palmitic acid, stearic acid or oleic acid as an emulsion aid, and an antioxidant such as cholesterol or dibutylhydroxytoluene, α-tocopherol or an ester thereof, for the purpose of stabilization, can be added as appropriate.

[0017] The active ingredient in the present invention is a substance represented by general formula (1) above; these are compounds known as aculeacin antibiotics (JP 59-20350 B1 to 59-20353 B1; *Tetrahedron Letters*, 4147-4150 (1976); *Helv.*

Chim. Acta **62** (4), 1252-267 (1979); JP 3-240727 A and JP 4-99721 A).

[0018] Examples of group R_1 in the general formula representing the active ingredients above are listed below.

[0019]

[Formula 5]

$-(CH_2)_nMe$ $(n=10\sim20)$、

$-(CH_2)_nCH=CH(CH_2)_7Me$

$(n=7、9、11)$、

$-(CH_2)_7CH=CH(CH_2)_7Me$、

$-(CH_2)_7CH=CH(CH_2)_8Me$、

$-(CH_2)_8CH=CH(CH_2)_{10}Me$、

$-(CH_2)_7CH=CHCH_2CH=CH(CH_2)_4Me$、

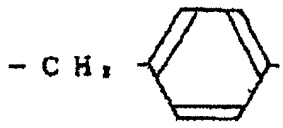
$-(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2Me$、

$-(CH_2)_8CH(Me)-CH_2CH(Me)-CH_2Me$、

$-(CH_2)_{12}NHCO(CH_2)_nMe$

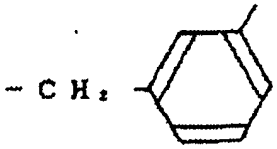
$(n=5、10)$、

$-(CH_2)_8NHCO(CH_2)_{10}Me$、



$-CH_2-O(CH_2)_nMe$

$(n=7、9、11)$、

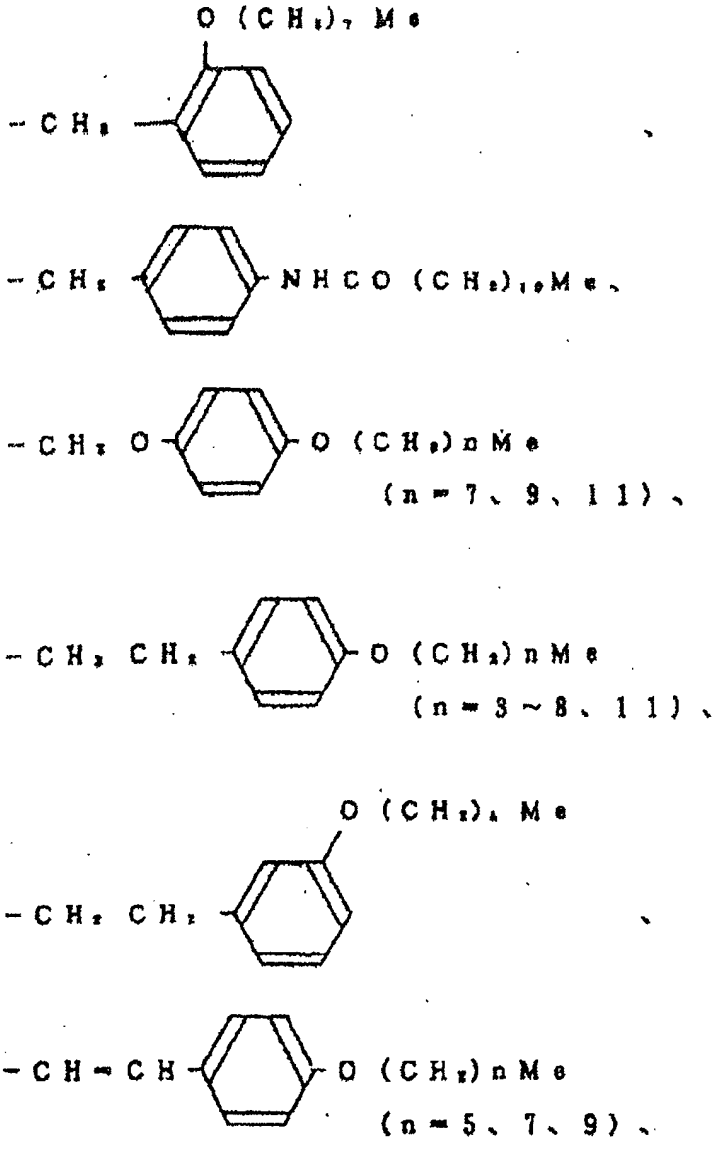


$O(CH_2)_nMe$

$(n=7、11)$

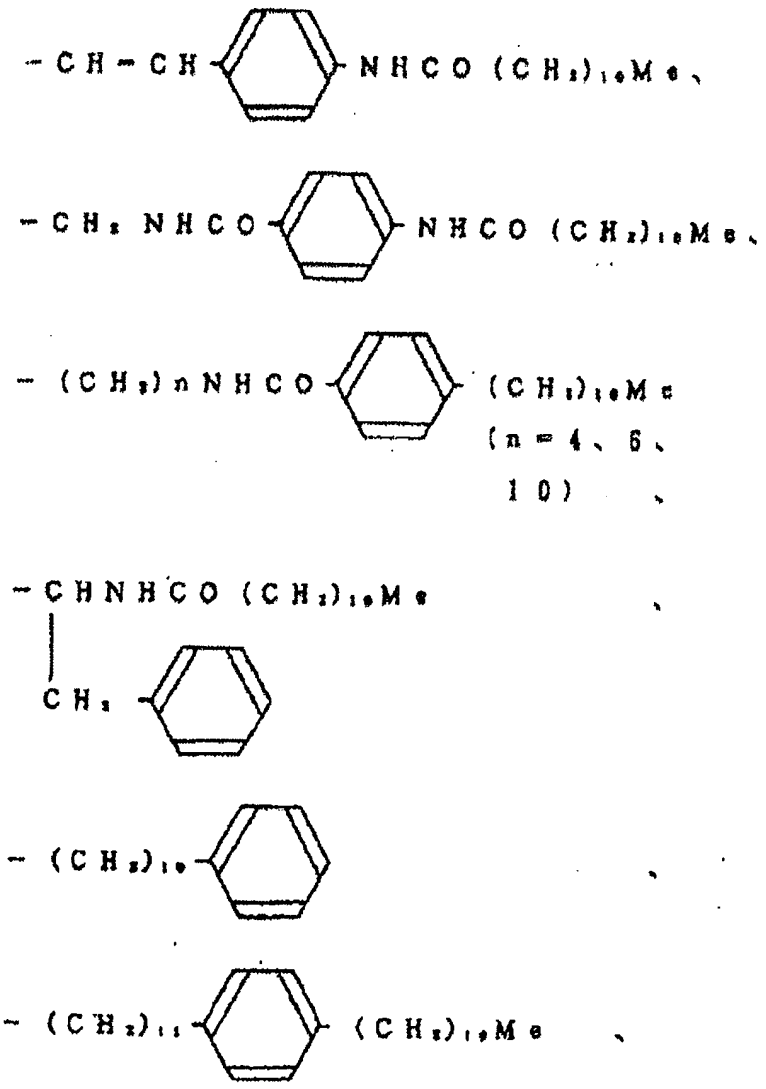
[0020]

[Formula 6]



[0021]

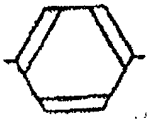
[Formula 7]



[0022]

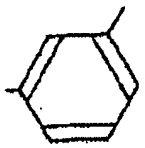
[Formula 8]


$(CH_2)_7Me$ 、

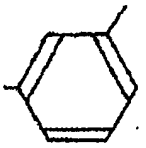

$O(CH_2)nMe$ ($n=5$、7、9、11、13、17)、


$S(CH_2)nMe$ ($n=7$、9、11、13)、


$SO_2(CH_2)nMe$ ($n=7$、9、11、13)、

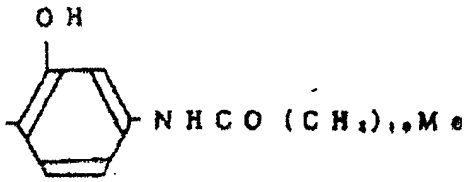

$O(CH_2)nMe$ ($n=7$、9、11、13)、


$NHCO(CH_2)nMe$ ($n=0$、5、8、10、12、14)、


$NHCO(CH_2)_{16}Me$

[0023]

[Formula 9]



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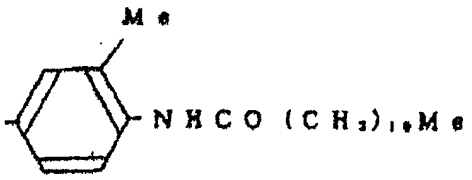

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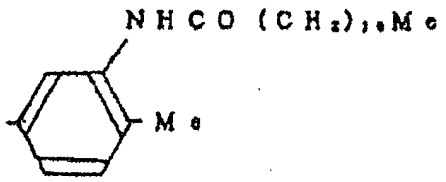

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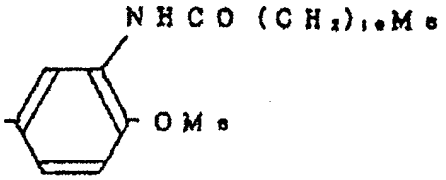

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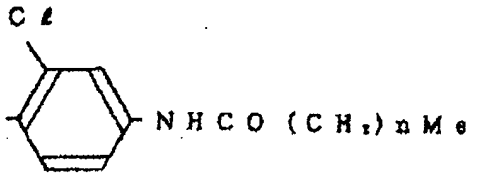

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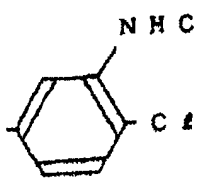
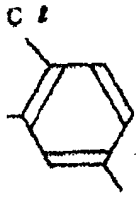
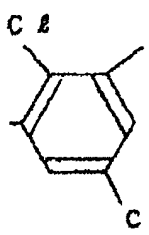
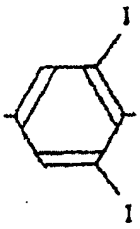
[0024]

[Formula 10]



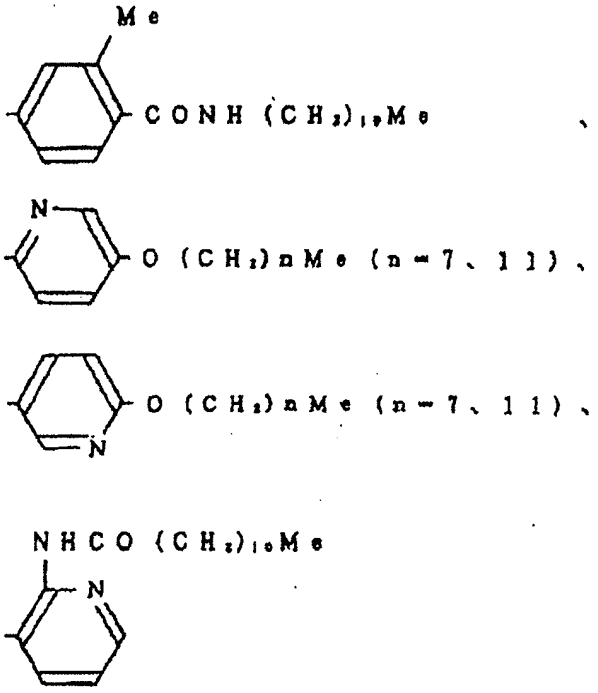






[0025]

[Formula 11]



[0026] Examples of R_2 include a hydrogen atom, a straight-chain or branched-chain C1-6 lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *t*-butyl, pentyl, hexyl, 3-methylbutyl, 2-ethylbutyl and 1-ethylbutyl, a benzyl group, an amino(lower alkyl) group such as 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 2-aminopropyl or 2-aminobutyl, and an amino(lower alkyl) group such as 2-aminoethyl or 3-aminopropyl in which the amino is monosubstituted with a lower alkyl group or disubstituted with lower alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or *sec*-butyl.

[0027] Group R_3 can be a hydrogen atom or $-CONH_2$, and group R_4 can be a hydrogen atom or a hydroxyl group. An aculeacin derivative is preferred wherein, in the aculeacin compound represented by general formula (1) above R_1-CO- is a long-chain saturated or unsaturated fatty acid residue, of C14-C18 for example, R_2 is a hydrogen atom, R_3 is a hydrogen atom and R_4 is a hydrogen atom or a hydroxyl group, and in the aculeacin derivative, aculeacin Aα, in which R_1-CO- is a myristic acid residue (C14) and R_4 is a hydroxyl group, aculeacin Aγ, in which R_1-CO- is a palmitic acid residue (C16) and R_4 is a hydroxyl group, aculeacin Dα, in which R_1-CO- is a myristic acid residue and R_4 is a hydrogen atom, aculeacin Dγ, in which R_1-CO- is a palmitic acid residue of aculeacin derivatives and R_4 is a hydrogen atom, are more preferred examples; other examples include echinocandin C, in which R_1-CO- is a stearic acid residue (C18), and R_4 is a hydrogen atom, and echinocandin B, in which R_1-CO- is a linoleic acid residue (C18, 2 double bonds), and R_4 is a hydroxyl group.

[0028] Examples of aqueous media in a fat emulsion of the present invention include water, and ideally injectable distilled water, or an aqueous media containing a polyhydric alcohol such as glycerin, glucose, sucrose or maltose as an isotonic agent at the order of 0.01-0.3M, at 2-100 parts by weight and preferably 8-20 parts by weight to 1 part by weight of liquid triglyceride.

[0029] Next, as a method for preparing fat emulsions of the present invention, for example the aforementioned active ingredient can first be thoroughly blended with the phospholipid and liquid triglyceride, and can easily be thoroughly mixed and blended in a mortar, or they can be blended in a mixer such as a ribbon blender. Then, using the aqueous medium at 2-100 parts by weight and preferably 8-20 parts by weight to 1 part by weight of liquid triglyceride, this blend is then mixed with the aqueous medium, with thorough dispersion treatment in a mortar, for example, being adequate for small-scale mixing, and dispersion using a homogenizer or kneader, etc., being appropriate for larger scale. This dispersed mixture can then be subjected to further high-speed stirring, in a homogenizer for example, for 4-10 minutes at 10,000 to 30,000 rpm. After this, the stirred liquid mixture can be emulsified; emulsification can be performed, for example, by ultrasound treatment with emulsification in an ultrasound homogenizer at 10-50 kHz for the order of 60-10 seconds, or high pressure emulsification with emulsification in a microfluidizer at a pressure of 300-1600 kg/cm^2 for about 15-50 cycles, and by so doing it is possible produce large quantities of an aculeacin-containing fat emulsion which is the object of the invention.

[0030] Fat emulsions of the present invention obtained in this way have a composition comprising the active ingredient at 0.001-50 mg/ml of the emulsion, and a

phospholipid at 0.01-1 part by weight and aqueous medium at 2-100 parts by weight to 1 part by weight of liquid triglyceride. The resulting fat emulsions also form extremely uniform liposomal particles, and by treatment with a 0.22-μm bacteria-removing filter, for example, they can be easily rendered aseptic, to give aseptic injectable preparations, and these can be used in suitable formulations. Moreover, the average particle size of the fat emulsion, measured by laser light scattering is preferably 50 nm to 300 nm, and it can give preparations containing high concentrations of aculeacin compounds of 50 mg/ml and can offer efficacious preparations. Fat emulsions of the present invention can be injected intravenously, intramuscularly, subcutaneously or endodermally, etc., or administered orally, applied to the mucous membrane of the oral cavity, nose, lungs, rectum or vagina, etc., or applied percutaneously. The preferred pH range of fat emulsions of the present invention is 3-10, with 5-8 being more preferred; and for the purposes of formulation suitable preservatives such as a paraben, phenol, benzalkonium chloride or benzetonium chloride, and isotonic agents, for example salts such as sodium chloride or potassium chloride, sugars such as glucose or sucrose, or polyhydric alcohols such as propylene glycol or glycerin, can be used.

[0031]

[Examples] The present invention is described in specific terms below by citing practical examples thereof; however, the present invention is not restricted in any way thereby.

[0032]

[Example 1] 5 g of purified egg yolk lecithin (Asahi Chemical Industries, Lot No. 88100261), 5 g of aculeacin Aγ and 10 g of soybean oil (Japanese Pharmacopoeia grade) were thoroughly blended for 3 minutes in a mortar, and then dispersed by adding an aqueous solution of 2 g of glycerin dissolved in 90 ml of purified water. This dispersion was then formed into a crude emulsion in a high-speed homogenizer (Biomixer BM-1; Nippon Seiki) at approximately 20,000 rpm for approximately 6 minutes and emulsified in an ultrahigh-pressure homogenizer (Microfluidizer M-110T; Microfluidics Corporation) at a pressure of 840 kg/cm^2 for approximately 20 cycles, to obtain a fat emulsion. Next, this was sterilized by filtration through a 22-μm membrane filter to give an injectable preparation.

[0033] The content of aculeacin Aγ in the liposome preparation after preparation was measured using high-performance liquid chromatography (HPLC). The average particle size of the liposome preparation was also measured by laser light scattering. The liposome suspension prepared had an aculeacin Aγ content of 45.0 mg/ml and an average

particle size of 159.8 ± 81 nm, and a preparation was obtained in which the aculeacin Aγ was homogeneously dissolved.

[0034]

[Example 2]

Stability test

2.5 g of purified egg yolk lecithin, 0.5 g of aculeacin Aγ and 5 g of soybean oil were thoroughly blended for 3 minutes in a mortar, and then dispersed by adding an aqueous solution of 1 g of glycerin dissolved in 45 ml of purified water. This dispersion was then treated as in example 1, to obtain an aseptic filtered fat emulsion. The preparation was stored at 4ºC and 25ºC for four weeks after preparation, and residual aculeacin Aγ (taking aculeacin Aγ content at the time of preparation as 100.0%) and average particle size were measured over time after 2 weeks and after 4 weeks.

[0035] The results are presented in Table 1.

[0036]

[Table 1]

Temperature/Time		Residual (%)	Particle size (nm)
At preparation		100.0	147.8 ± 61
4ºC	2 weeks	96.7	146.9 ± 73
	4 weeks	95.2	147.5 ± 53
25ºC	2 weeks	95.7	147.5 ± 74
	4 weeks	90.1	148.3 ± 48

[0037] As indicated in Table 1, the percentage of residual aculeacin Aγ after 4 weeks was greater than 95% at 4ºC and greater than 90% at 25ºC. As regards average particle size, a stable particle size of about 145 nm was maintained for 4 weeks at both 4ºC and 25ºC. Therefore, the liposome preparation obtained had good long-term storage stability at 4ºC.

[0038]

[Example 3] 2.5 g of purified egg yolk lecithin, 0.5 g of aculeacin Aγ and 5 g of soybean oil were thoroughly blended for 3 minutes in a mortar, and then dispersed by adding an aqueous solution of 2.5 g of glucose dissolved in 45 ml of purified water. This dispersion was then treated as in example 1, to obtain an aseptic filtered fat emulsion. The average particle size of the resulting fat emulsion was 151.8 ± 75 nm.

[0039]

[Example 4] 0.5 g of purified egg yolk lecithin, 0.1 g of aculeacin Aγ and 1 g of medium-chain fatty acid triglyceride (Triester F810; Nippon Surfactant) were used and thoroughly blended for 3 minutes in a mortar and then dispersed by adding an aqueous solution of 0.2 g of glycerin dissolved in 10 ml of sterile distilled water. Next this dispersion was formed into an emulsion in a high-speed homogenizer (Biomixer BM-1; Nippon Seiki) at approximately 20,000 rpm for approximately 6 minutes and then homogenized

in an ultrasonic homogenizer (Nippon Seiki, model U-300) inside a stainless steel container containing ice, by treatment for 30 cycles of approximately 20 kHz for 20 seconds followed by resting for 10 seconds to obtain a liposomal suspension, which was sterilized by filtration through a 0.22-μm membrane filter to obtain a fat emulsion with an average particle size of 142.6 ± 82 nm.

[0040]

[Example 5] The procedure of example 1 was repeated using 1 g of purified egg yolk lecithin and 0.2 g of aculeacin Aα to prepare an aseptic filtered fat emulsion.

[0041]

[Example 6] The procedure of example 1 was repeated using 1 g of purified egg yolk lecithin and 0.2 g of aculeacin Dα to prepare an aseptic filtered fat emulsion.

[0042]

[Example 7] The procedure of example 1 was repeated using 1 g of purified egg yolk lecithin and 0.2 g of aculeacin Dγ to prepare an aseptic filtered fat emulsion.

[0043]

[Effects of the invention] As described above, by means of the present invention it becomes possible to prepare stable fat emulsions having as an active ingredient a high content of an aculeacin compound sparingly soluble in water and liquid triglycerides, and as a result it becomes possible

to offer preparations efficacious for preventing and treating *Pneumocystis carinii* pneumonia.